

Remarks/Arguments

Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Continuity

Applicants maintain that the present invention has utility based on the gene amplification assay for the PRO1153 molecule and its antibodies that meets the utility standards set by the USPTO and for the reasons discussed below. Applicants maintain that this utility was first disclosed in U.S. Provisional Application 60/141037, filed June 23, 1999, priority to which has been claimed in this application. Hence, Applicants are entitled to the benefit of the above provisional application and accordingly, to an effective filing date of at least **June 23, 1999**.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 allegedly “because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility.”

Claims 119-123 remain further rejected under 35 U.S.C. §112, first paragraph allegedly “since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention”.

The Examiner acknowledges that the specification provides data but asserts that it shows a "very small increase in DNA copy number- about 2.5 fold- in a single type of tumor". The Examiner also alleges that there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are increased in this cancer. The Examiner cites Hu *et al.* and says that "literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. According to the Examiner, Hu shows that "for genes displaying 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease". The Examiner further asserts that the Polakis and the Ashkenazi declarations were insufficient to overcome the rejections of claims 119-123 because "no evidentiary support was provided as to whether the gene products are over-expressed or not" and further because there is "no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology

that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide". The Examiner maintains that Pennica *et al.*, and Haynes *et al.* show that "polypeptide levels cannot be accurately predicted from mRNA levels". Applicants respectfully traverse this rejection for the reasons provided below.

Utility – Legal Standard

In interpreting the utility requirement, in *Brenner v. Manson*¹ the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."² The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."³

Later, in *Nelson v. Bowler*⁴ the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."⁵

In *Cross v. Iizuka*⁶ the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e.

¹ *Brenner v. Manson* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

² *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

³ *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

⁴ *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

⁵ *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

⁶ *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

there is a reasonable correlation there between."⁷ The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."⁸

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.⁹ The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.¹⁰ In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."^{11, 12}

Compliance with 35 U.S.C. §101 is a question of fact.¹³ The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.¹⁴ Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

⁷ *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

⁸ *Id.*

⁹ *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

¹⁰ *Ibid*

¹¹ *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

¹² See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

¹³ *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

¹⁴ *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

The well established case law is clearly reflected in the Utility Examination Guidelines (“Utility Guidelines”) ¹⁵, which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.” Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a “‘substantial’ utility.” ¹⁶ Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, ¹⁷ gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1153 polypeptide of SEQ ID NO:351 and antibodies thereof.

In particular, the gene amplification assay discloses that the nucleic acid encoding PRO1153 is significantly overexpressed in human tumor tissues as compared to a non-cancerous human tissue control. Table 8 explicitly states that PRO1153 is significantly overexpressed in lung adenocarcinoma tumors as compared to the normal control. The specification further

¹⁵ 66 Fed. Reg. 1092 (2001).

¹⁶ M.P.E.P. §2107.01

¹⁷ M.P.E.P. §2107 II (B) (1)

teaches that these data demonstrate that the PRO1153 polypeptide of the present invention is also useful as a diagnostic marker for the presence of one or more lung adenocarcinoma tumors in which it is significantly overexpressed. The above disclosure is sufficient to establish a specific, substantial and credible utility for the PRO1153 polypeptide.

Applicants respectfully maintain that, for the reasons previously set forth in the Applicants' response filed July 16, 2004, Pennica *et al.* and Haynes do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. For example, Pennica discusses WISP genes only, and not genes in general, and therefore it does not teach that *it is more likely than not* that gene amplification is not associated with increased mRNA or increased protein levels.

In fact, Haynes, contrary to the Examiner's reading, teaches that "there was a *general trend but no strong correlation* between protein [expression] and transcript levels" (Emphasis added) even though protein levels could not be accurately predicted. For example, in Figure 1, there is a positive correlation between mRNA and protein levels amongst most of the 80 yeast proteins studied. In fact, very few data points deviated or scattered away from the expected normal and no data points showed a negative correlation between mRNA and protein levels (i.e. an increase in mRNA resulted in a decrease in protein levels). As discussed above, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the Haynes data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in Haynes *et al.*, and application of an improper, heightened legal standard.

Further, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level as was discussed in the three previously presented articles, Orntoft, Hyman and Pollack *et al.* The data presented in these three papers clearly showed that "*it is more likely than not*" that a gene which is amplified in tumor cells will have increased gene expression.

According to the Examiner, Hu *et al.* shows that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation

between altered gene expression and a known role in the disease. Hu teaches that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. Applicants further respectfully submit that the Hu et al. reference does not show a lack of correlation between gene amplification data and the biological significance of cancer genes, for the reasons outlined below.

As a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, as the Examiner suggests, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

First, the analysis by Hu et al. has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Secondly, Applicants submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusions based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and **can not be generalized as a principle governing microarray study of breast cancer in general**, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that ., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). Therefore, the Hu reference is not appropriate since again, it too does not teach that it is more likely than not, for genes in general, that DNA amplification does not result in increased protein levels.

For added support, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, which discusses the correlation between mRNA expression and protein levels, and shows that mRNA expression correlates well with protein levels, in general, based on Dr. Polakis' vast experience of more than 20 years and based on the microarray analysis results of approximately 200 gene transcripts (mRNAs) from various gene families. Applicants maintain that the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard, the proper legal standard being only that the showing of correlation between mRNA and polypeptide levels be "more likely than not."

The Office Action states that the Dr. Polakis Declaration is insufficient to overcome the rejection and notes that "the instant specification provides no information regarding increased mRNA levels of PRO1153 in tumor samples as contrasted to normal tissue samples: Only gene amplification levels were presented". Applicants agree but indeed, if the Polakis Declaration were not relevant, then neither should the Hu *et al.* reference cited by the Examiner, since Hu also concerns the correlation between mRNA and protein levels, as discussed above.

Further, the Office action alleges that only Dr. Polakis' conclusions are provided in the Declaration. There was allegedly no evidentiary support for Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide".

Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.¹⁸ "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a

¹⁸ *In re Rinehart* 531 F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985).

preponderance of the evidence with due consideration to persuasiveness of argument" ¹⁹

Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" ²⁰. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines ²¹ which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statement in question from an expert in the field (the Polakis declaration) states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines.

The Office Action also says that the Ashkenazi declaration is insufficient to overcome the instant rejection because "only Dr. Ashkenazi's conclusions are provided.... there is no evidentiary support...".

Again, as discussed above in the Utility guidelines and the arguments provided under the Polakis declaration, "it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." In Dr. Ashkenazi's opinion, even if the protein were not over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. To support this reasoning of Dr. Ashkenazi, Applicants had submitted the article by Hanna and Mornin, to demonstrate that, as in the example of the HER-2 gene, testing both gene and gene product (protein) lead to a more accurate classification of the cancer and more effective tumor treatment.

In response to the Examiner's comment that "the skilled artisan would need to perform additional experiments,.....the asserted utility for PRO1153 polypeptides and claimed antibodies

¹⁹ *In re Alton* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

²⁰ *In re Alton*, supra.

²¹ Part IIB, 66 Fed. Reg. 1098 (2001).

is not in currently available form, the asserted utility is not substantial," Applicants once again draw the Examiner's attention to the Utility guidelines regarding "substantial utility" which cautions:

".... Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." (emphasis added) M.P.E.P. §2107.01.

Applicants submit that, based on the results presented in the gene amplification assay for PRO1153 DNA, one skilled in the art would know that the corresponding polypeptide and antibodies have credible, specific and substantial asserted utility, for example, in detecting over-expression or absence of expression of PRO1153. This conclusion would be based on the art which indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. None of the references provided by the Examiner compellingly met the standard for most genes or gene classes in general. Instead, the references either referred to a single, few or a singular class of gene(s) with a lack of correlation between DNA and protein levels. In fact, some of the references referred to statistical analysis of data, where data had to be selected to provide meaningful interpretations. In the process, representation of "most genes" was lost and thus, conclusions can only be applicable to a particular class of genes studied (for example, breast cancer genes in Hu et al.).

Correspondingly, Applicants provided evidence to meet the "more likely than not standard" and Declarations by experts based on their personal experience and/or literature articles as to why utility is credible. The additional experiments, if any, are routine in the art, based on the teachings in the specification and the knowledge of the skilled artisan, at the time the application was filed.

¹⁶ M.P.E.P. §2107.01


Thus, Applicants maintain that they have demonstrated utility for the PRO1153 polypeptide and antibodies thereof as diagnostic markers for detecting adenocarcinomas or squamous cell carcinomas of human lung. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C32). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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